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14. ABSTRACT

The possible role of histone deacetylase inhibitors (HDACi) in breast cancer treatment is an area of active investigation. However, its potential as a preventive agent has not been studied. Valproic acid (VPA) is an HDACi which has been used for many decades to safely treat neurological disorders. The rationale for the use of HDACi in breast cancer prevention is a previously unexplored area of research that is based on compelling preclinical data. Epidemiologic studies showing an association between HDACi use and breast cancer incidence would be important evidence to support future prospective clinical trials of HDACi in cancer prevention. **The aim of this project is to ascertain whether the risk of incident breast cancer is reduced in patients with a history of VPA use, and if so, to determine whether this effect is proportional to the duration of VPA use and whether all subtypes of breast cancer are impacted similarly.** We have developed a database using de-identified data from the Kaiser Permanente of Northern California (KPNC) clinical and pharmacy records between 1997 and 2007. 22,488 breast cancer cases and 224,860 controls have been identified. Controls have been matched to cases

15. SUBJECT TERMS

breast cancer, prevention, valproic acid, histone deacetylase inhibitors, epigenetics

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ABSTRACT

The possible role of histone deacetylase inhibitors (HDACi) in breast cancer treatment is an area of active investigation. However, its potential as a preventive agent has not been studied. Valproic acid (VPA) is an HDACi which has been used for many decades to safely treat neurological disorders. The rationale for the use of HDACi in breast cancer prevention is a previously unexplored area of research that is based on compelling preclinical data. Epidemiologic studies showing an association between HDACi use and breast cancer incidence would be important evidence to support future prospective clinical trials of HDACi in cancer prevention. **The aim of this project is to ascertain whether the risk of incident breast cancer is reduced in patients with a history of VPA use, and if so, to determine whether this effect is proportional to the duration of VPA use and whether all breast cancer subtypes are impacted similarly.** We have developed a database using de-identified data from the Kaiser Permanente of Northern California (KPNC) clinical and pharmacy records between 1997 and 2007. 22,488 breast cancer cases and 224,860 controls have been identified. Controls have been matched to cases based upon birth year and duration of KNPC pharmacy coverage. Mean age at diagnosis of the cohort was 61 years; mean years of prescription drug coverage was 7 years. Among cases, 72% of the cohort was non-hispanic white, 8% were African American, and 11% were Asian/Pacific Islander. In the second year of the proposal, we will evaluate the prevalence and duration of valproic acid use among cases and controls to examine the association between valproic acid and breast cancer risk. The few noninvasive preventive measures that exist for breast cancer have limited uptake, even among women at increased risk. Thus, other preventive agents, particularly those that may impact ER-negative as well as ER-positive disease, are critically needed, as is epidemiologic evidence of preventive effect.

INTRODUCTION

The possible role of histone deacetylase inhibitors (HDACi) in breast cancer treatment is an area of active investigation(1-5). However, its potential as a preventive agent has not been studied. Valproic acid (VPA) is an HDACi which has been used for many decades to safely treat neurological disorders. The rationale for the use of HDACi in breast cancer prevention is a previously unexplored area of research that is based on compelling preclinical data, that shows that VPA reduces risk of invasive breast cancer in animal models(1). Epidemiologic studies showing an association between HDACi use and breast cancer incidence would be important evidence to support future prospective clinical trials of HDACi in cancer prevention. **We hypothesize that the risk of incident breast cancer is reduced in patients with a history of VPA use, and that this effect is proportional to the duration of VPA use. The Specific Aims we plan to achieve are the following: Aim 1:** We will compare the incident breast cancer rate in women with a history of valproic acid use to an age-matched cohort without VPA use, adjusting for potential confounders. We will establish whether VPA is associated with a reduced risk of breast cancer in this cohort, and whether duration of therapy impacts this risk. **Aim 2:** We will determine whether the association between VPA use and incident breast cancer differs among patient populations and tumor subtypes. If feasible, we will examine this association among different race/ethnicities as well as evaluate the tumor characteristics associated with VPA use.

BODY

During the past year, we have evaluated members within the Kaiser Permanente system in Northern California (KPNC), a closed system which provides and tracks all prescription medications provided to its members throughout the period of plan membership. Although initiation of data collection has been significantly hampered by an unanticipated turnover in programming personnel, progress has been made towards achieving our stated aims within the timeframe of the 1-year no-cost extension. Progress to date includes the following:

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- Identification of cases and controls: Cases status was determined as those female members identified by the KPNC Cancer Registry as having a diagnosis of invasive breast cancer with known ER status between 1997 and 2007.

- Cases were matched to controls on the basis of year of birth and duration of KPNC pharmacy coverage. 22,488 breast cancer cases and 224,960 controls have been thus identified. Among cases, 3,996 cases were found to be ER-negative, and 18,492 were ER-positive.

- VPA formulations carried by the KPNC pharmacy were identified and consisted of valproic acid, valproate sodium, and divalproex sodium. ICD-9 codes for indications for use have also been identified: epilepsy/seizure disorder (345.0-345.9/780.39), depression (296.2, 296.3, 311), and migraine (346.0=346.9).

- Use of exogenous hormones in this population has also been collected in the database.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

Will be forthcoming upon completion of data collection and analysis.

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

Will be forthcoming upon completion of data collection and analysis.

Expected outcomes and potential pitfalls: the expected number of new cancer diagnoses in this managed care population is over 2000 incident cases per year. However, the number of women taking VPA in this cohort is unknown. To determine a relative risk reduction of 30% with 80% power, and α of 0.05 and assuming an annual incidence rate of 3/1000 in this population, we will require approximately 3500 patients with a history of VPA use with a 2:1 matching of controls to cases. If the number of patients with a history of VPA is insufficient to adequately power this study (Task 1a), we will extend data collection to include other geographic catchment areas of this managed care group. Other outcome and predictor variables are known to have been collected in this data registry.

Facilities and Resources

Primary data retrieval will continue to be performed at the Division of Research at Northern California Kaiser. All other study-related activities will be conducted at the UCSF Cancer Center, which houses the research staff for the UCSF Breast Care Center. Sufficient space, computer, and IT resources exist to support the conduct of this study.

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